REMARKS

Claims 1, 3, 5-10 and 12-14 are pending in this application.

Claim 10 has been amended to recite "consisting essentially of" in order to be consistent with claims 1 and 13.

I. Personal Interview

Applicant appreciates the courtesies extended to Applicant's attorneys by Examiner Frazier and Supervisory Examiner Blanchard during the personal interview held June 26, 2012.

Applicant's attorneys traversed the outstanding prior art rejection based upon the arguments presented in the Amendment After Final Rejection filed April 24, 2012, and presented new arguments to traverse the Examiner's arguments presented in the Advisory Action dated May 2, 2012 (discussed below).

Examiner Frazier maintained the rejection, and asserted that even though there is a showing of unexpected results in Example 1 of the specification, and claims 1 and 13 recite "consisting essentially of" language to exclude Carbopol, the *prima facie* case of obviousness has not been overcome.

In addition, Examiner Frazier stated that she has performed another prior art search, and found that US 2003/0139436 teaches to use a water-soluble metal chloride for light-stabilizing effects.

New claim 14 was also discussed. Examiner Frazier stated that she has not fully examined this claim to determine whether it is patentable over the art, but it appears allowable over the references of record.

Applicant greatly appreciates the Examiners' comments, and has considered these comments in preparing this Supplemental Amendment.

II. Claim Rejection Under 35 U.S.C. § 103

The Examiner has rejected claims 1-10, 12 and 13 under 35 U.S.C. § 103(a) as being unpatentable over Kita et al. (US 6,307,052) in view of Lehmussaari et al. (US 5,795,913). As applied to the amended claims, Applicant respectfully traverses the rejection.

A. The Examiner's Position

The Examiner has asserted that Kita et al. disclose (+)-(S)-4-[4-[(4-chlorophenyl)(2-pyridyl)methoxy]piperidino] butyric acid or a benzenesulfonic acid salt thereof (hereinafter, "bepotastine"), but do not disclose how a composition comprising bepotastine is formulated and

do not disclose a composition comprising bepotastine and a water-soluble metal chloride in a light-stabilizing effective amount of 0.2 w/v% to 1.2 w/v%. The Examiner applies Lehmussaari et al. for disclosing sodium chloride and potassium chloride in an amount of 0.01 to 2.0% by weight. See final Office Action, pages 2-3.

B. Carbopol

Claims 1, 10 and 13 each recite the transitional phrase "consisting essentially of", which limits the scope of a claim to the specified materials or steps and those that do not materially affect the basic and novel characteristic(s) of the claimed invention (see MPEP 2111.03).

The composition of Lehmussaari et al. requires the inclusion of an ion sensitive, hydrophilic polymer having viscosity, such as **Carbopol**, to control the formation of the polymer film on the cornea of the eye, and each of the reference's examples contain Carbopol (please see col. 2, line 57 to col. 3, line 6, and the Examples).

Carbopol is degraded by light. This is clear from the Chemical Abstract reference dated January 3, 1972 enclosed with the Amendment filed April 24, 2012, and the enclosed Declaration under 37 CFR 1.132. As requested by the Examiner, the Chemical Abstract reference is submitted again herewith in an Information Disclosure Statement.

As discussed in the Declaration, the reference states "CARBOXYVINYL POLYMERS of the type Carbopol 940…and 941 were degraded by light, type 941 presenting the highest DEGRADATION" (emphasis in original). This clearly teaches that it was known that Carbopol is degraded by light well-prior to the U.S. filing date of the present application (2003).

Using an ion sensitive, hydrophilic polymer, such as Carbopol, in the aqueous liquid preparation of claim 1 and the eye drops of claims 10 and 13 would materially affect the basic and novel characteristics of the claimed compositions, because it would introduce a component that degrades in light into a composition that is designed to be "light-stabilized" by a water-soluble metal chloride.

As a result, an ion sensitive, hydrophilic polymer is **excluded** from the aqueous liquid preparation of claim 1 and the eye drops of claims 10 and 13. Therefore, a person of ordinary skill in the art could not have arrived at the presently claimed invention from the combination of Kita et al., disclosing bepotastine, and Lehmussaari et al., disclosing a metal chloride in a composition with Carbopol, with any reasonable expectation of success.

C. Unexpected Results

In the Advisory Action, the Examiner has asserted that even though Applicant has demonstrated a critical range in which sodium chloride, potassium chloride or calcium chloride impart a light-stabilizing effect on bepotastine, a person of ordinary skill in the art would have arrived at 0.2-1.2 w/v% of the metal chloride by routine experimentation.

However, under MPEP 2144.05.II.B, "[a] particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation".

The Lehmussaari et al. reference provides no teaching that varying the salt concentration would be helpful for light-stabilization or viscosity optimization. The reference states, "[a]ccording to the invention we have shown that it is **the amount of polymer in the composition, rather than the viscosity of the composition** as such, which are important from the point of view of obtaining good absorption of drug into the eye". Fig. 3 shows that by using the same amount of polymer, in compositions that have different viscosities, the compositions provide for substantially the same absorption. Fig. 4 shows that compositions containing different amounts of polymer but the same viscosities and pH's have stronger absorption over the composition with the higher polymer concentration. See col. 2, lines 19-34.

One skilled in the art might have recognized that the result-effective variable in the reference is the amount of **polymer (carbopol)**, but could not have recognized at all that the amount of **salt** is a result-effective variable. Therefore, one skilled in the art would not consider the salt concentration to be a result-effective variable, and would not have determined the optimum concentration by routine experimentation.

In addition, in Experimental Example 1 of the specification, Formulation 2, comprising **0.1 w/v%** of a metal chloride (sodium chloride) **fails** to light-stabilize bepotastine besilate, because after light irradiation it was slightly dark green-pale yellow and produced a precipitate. On the other hand, Formulations 3-6, comprising **0.2 to 1.18 w/v%** of a metal chloride (i.e., sodium chloride, potassium chloride or calcium chloride), provide an unexpected light-stabilizing effect, because after light irradiation the formulations were pale yellow and clear and no precipitate was formed.

The fact that Formulation 2, comprising **0.1 w/v%** of a metal chloride (sodium chloride), does not light stabilize the composition, even though it falls within the reference's broad range, is evidence that the reference's salt range (0.01-2.0 %) would **not** be expected to light-stabilize a composition comprising bepotastine.

Therefore, the Examiner has failed to consider the showing of unexpected results.

D. Conclusion of Non-Obviousness

As stated in MPEP 2145, the Examiner **must consider all rebuttal arguments and evidence** presented by Applicant (citing *In re Soni*, 54 F.3d 746, 750, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995)).

Claims 1, 10 and 13 recite "consisting essentially of", which clearly excludes the required ingredient of Carpobol of Lehmussaari et al., because it would materially affect the basic and novel characteristics of the claimed invention.

Furthermore, the present specification demonstrates that a water-soluble metal chloride in an amount of 0.2 w/v% to 1.2 w/v% has an unexpected light-stabilizing effect.

Therefore, claims 1, 10 and 13 would not have been obvious over the combination of Kita et al. and Lehmussaari et al.

Claims 3, 5-9 and 12 depend from directly or indirectly from claim 1, and thus also would not have been obvious over the references.

Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

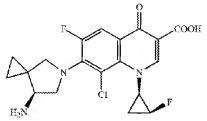
III. Araki et al.

During the interview, the Examiner cited Araki et al. (U.S. Patent Application Publication No. 2003/0139436). Applicant submits the enclosed Declaration, which includes the following remarks to distinguish over this reference.

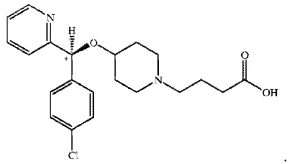
A. The Differences Between Bepotastine and Sitafloxacin

Araki et al. disclose a composition comprising sitafloxacin (see abstract). Sitafloxacin has a completely different chemical structure and has completely different chemical properties as compared to bepotastine, which is contained in the claimed compositions.

Sitafloxacin has the following chemical structure:



Bepotastine has the following chemical structure:



The compounds clearly have different chemical structures, and virtually no similar chemical moieties. For example, sitafloxacin has an oxoquinoline core bonded to a cyclopropyl group and a azaspiro[2,4]heptan group. On the other hand, bepotastine does not have any bicyclic or spiro rings, and has separate pyridine and piperidine rings. There are no common chemical groups in the two compounds that would suggest they share any similar activity or have any similar properties.

Araki et al. disclose light stabilization of sitafloxacin by sodium chloride. Sodium chloride is generally used for isotonization.

Since sitafloxacin has a completely different chemical structure and completely different chemical properties as compared to bepotastine, as discussed above, there is no predictability or correlation of light stabilization of bepotastine by sodium chloride.

Therefore, one skilled in the art would not expect a metal chloride to have a light-stabilizing effect on bepostatine in view of the light stabilizing effect of sodium chloride on sitafloxacin.

B. There is No Reasonable Expectation that Sodium Chloride Would Suppress Coloration and Precipitation of Bepotastine in view of Araki et al.

Araki et al. state the following:

[0100] As is understood from Table 1, the aqueous sitafloxacin solutions without sodium chloride or containing D-sorbitol in place of sodium chloride undergo reductions in pH, transmission and sitafloxacin content and an increase of related substances when irradiated.

[0101] However, it is apparent that addition of sodium chloride suppresses these unfavorable changes due to irradiation, showing improvement on sitafloxacin stability against light.

The reference is silent on the suppression of coloration and precipitation. While Araki et al. teach that the addition of sodium chloride results in the suppression of changes in transmission, the reference does not teach or suggest that sodium chloride causes coloration, and, likewise, does not mention the suppression of coloration by sodium chloride.

On the other hand, the present application demonstrates that when an aqueous bepotastine solution free of sodium chloride was subjected to light irradiation, the solution turned black green, and a precipitate was produced (see specification, page 8, lines 8-9, Formulation 1). A person of ordinary skill in the art with the goal of reducing or eliminating this phenomenon would not refer to the teachings Araki et al. and would not have been motivated by the teachings to Araki et al. to include a metal chloride in a bepotastine composition, because the reference provides no description regarding coloration and precipitation.

Accordingly, there would have been no reasonable expectation of success of arriving at the claimed invention from the disclosure of Araki et al.

Therefore, the aqueous liquid preparation of claim 1 and the eye drops of claims 10 and 13 would not have been obvious over Araki et al. in view of Kita et al. and/or Lehmussaari et al., or in view of any other reference.

IV. Claim 14

Claim 14 recites "consisting of". The transitional phrase "consisting of" excludes any element, step, or ingredient not specified in the claim (see MPEP 2111.03).

As recognized by the Examiner, none of the references disclose an aqueous liquid preparation consisting of, in an aqueous solution, an active ingredient consisting of (+)-(S)-4-[4-[(4-chlorophenyl)(2-pyridyl)methoxy]piperidino] butyric acid or a pharmacologically acceptable

acid addition salt thereof, a water-soluble metal chloride in a light-stabilizing effective amount, wherein the metal chloride has a concentration selected from the range of a lower limit concentration of 0.2 w/v% and an upper limit concentration of 1.2 w/v%, benzalkonium chloride, sodium dihydrogenphosphate dihydrate, sodium hydroxide and water.

Therefore, claim 14 is patentable over the cited references.

V. Conclusion

For these reasons, Applicant takes the position that the presently claimed invention is clearly patentable over the applied references.

Therefore, in view of the foregoing amendments and remarks, it is submitted that the rejection set forth by the Examiner has been overcome, and that the application is in condition for allowance. Such allowance is solicited.

Respectfully submitted,

Masayo HIGASHIYAMA

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Enclosures: Declaration under 37 CFR 1.132 and Information Disclosure Statement